

Long-Term Kidney Function, Proteinuria, and Associated Risks among HIV-Infected and Uninfected Men in the MACS

Frank J Palella Jr, Xiuhong Li, Samir K. Gupta, Michelle M. Estrella, John P. Phair, Joseph B. Margolick, Roger Detels, Lawrence Kingsley, and Lisa P. Jacobson

Abstract

Background: Factors affecting kidney function and proteinuria among HIV+ and HIV- persons need better characterization.

Methods: We evaluated estimated glomerular filtration rate (eGFR, mL/min per 1.73 m²) changes, proteinuria prevalence (a urine protein-to-creatinine ratio [UPCr] of ≥ 0.2 at two consecutive visits) and associated factors among HIV+ and HIV- men.

Results: There were 917 HIV+ men receiving HAART, 159 HIV+ men not receiving HAART, and 1305 HIV- men seen from 10/2003 to 9/2014. Median annual eGFR change was -0.5%, -0.8% for HIV+ and -0.3% for HIV- men ($p < 0.001$). Factors significantly ($p < 0.05$) associated with $> 3\%$ annual eGFR decline were: HAART receipt (but no specific ART drug), age > 50 , hypertension, diabetes, current smoking. Proteinuria existed in 14.9% of visit-pairs among HAART recipients, 5.8% among non-HAART recipients, and 1.9% among HIV- men, and was associated with subsequent annual $> 3\%$ eGFR decline (OR 1.80, $p < 0.001$). Proteinuria-associated factors also included HAART use (vs. HIV-), age ≥ 50 (vs. < 40), diabetes, hypertension, current smoking, HCV-infection (all

p<0.05) and, among HIV+ men, lower CD4 cell count, didanosine, saquinavir, or nelfinavir use (all p<0.05). After adjusting for proteinuria, among HAART users, having a detectable HIV RNA, cumulative use of tenofovir disoproxil fumarate (TDF), emtricitabine, ritonavir, atazanavir, any protease inhibitor, or fluconazole were associated with >3% annual eGFR decline.

Conclusions: Longitudinal kidney function decline was associated with HAART use but no individual ART drug, and traditional kidney disease risks. Proteinuria was nearly 7 times more common in HAART-treated men than HIV- men, reflected recent eGFR decline and predicted subsequent eGFR decline.

Word Count: 3601

Abstract Word Count: 249

Background

Kidney disease is an important cause of morbidity among HIV+ persons^[1-4]. While HIV itself is a known kidney pathogen^[5] and accounted for much kidney disease among HIV+ persons before the advent of highly active antiretroviral therapy (HAART)^[6], it is now clear that diverse multifactorial processes that can impact kidney function in HAART-treated HIV+ persons^[7-10]. Nuanced longitudinal characterization of kidney function over time and of factors impacting it among HIV+ persons receiving HAART is needed. Using an appropriate control group of HIV- but at-risk persons allows differentiation of HIV-specific risk factors from those that are not unique to HIV+ individuals, such as hypertension and diabetes mellitus. Likewise, the role of systemic inflammation in kidney disease development, particularly among HIV+ persons, requires better evaluation^[11-15]. These all are important to evaluate among HAART-treated virally-suppressed HIV+ persons, for whom survival has been extended and in whom chronic co-morbidities, aging, antiretroviral therapies, and systemic inflammation may contribute to the development and progression of kidney disease^[16-18].

Glomerular filtration rate estimates (eGFR) and urine protein-to-creatinine ratios (UPCR) are complementary indicators of kidney function and damage widely used for kidney disease screening and monitoring in the general population^[19]. While GFR estimates are standard monitoring tools in the management of HIV+ persons, quantitative assessments of proteinuria are less common, and concurrent examination of both are uncommon in this population.

In this report, we assessed factors impacting longitudinal kidney function and proteinuria among HIV+ and demographically similar HIV- men followed in the Multicenter AIDS Cohort Study (MACS).

Methods

The Cohort

The MACS^[20] is an ongoing multi-center, prospective study of men who have sex with men (MSM). MACS sites in Baltimore, MD-Washington, DC; Chicago, IL; Los Angeles, CA; and Pittsburgh, PA have enrolled a total of 6,972 men in 1984-85, 1987-90, and 2001-03. The MACS prospectively schedules participants for semi-annual study visits where medical and therapy histories, physical and behavioral assessments, and biological specimens are collected under standardized protocols. Individuals eligible for the current study were HIV+ and HIV-participants who contributed at least three serum creatinine (SCr) measurements from visit 40 (2003), when SCr was first measured in the study, through visit 61 (2014).

Hepatitis B virus (HBV) co-infection was determined by the presence of a positive hepatitis B surface antigen. Hepatitis C virus (HCV) co-infection was defined by a positive HCV RNA. HAART was defined in accordance with US Department of Health and Human Services (DHHS) treatment guidelines (www.aidsinfo.gov; November 2014 version) as use of three or more antiretroviral (ART) drugs including one or more of

protease inhibitors (PI), nucleoside reverse transcriptase inhibitors (NRTI), a non-nucleoside reverse transcriptase inhibitor (NNRTI), integrase inhibitor, or entry inhibitor (including fusion inhibitors). Information regarding the presence of traditional risk factors for CKD (eg hypertension, diabetes) were based on a combination of: 1) participant self-report; 2) study-obtained measurements; 3) medication usage.

Informed consent from each participant and approval from each local institutional review board were obtained.

Outcomes and Analytic Methods

The baseline visit was defined as the first visit with SCr data. Participants with incident HIV infection (n=93) or those HIV+ men who initiated HAART during the study period (n=124) were included as HIV- before HIV infection and HIV+ but not receiving HAART before HAART initiation, respectively. GFR was estimated in mL/min/1.73 m² using the serum creatinine-based CKD-EPI equation^[21]. Baseline characteristics of HIV- and HIV+ subject groups were compared using the Wilcoxon test or the Chi-square test, when appropriate. Cochran-Armitage Trend Test was used to examine trends in the prevalence of hypertension, diabetes mellitus, and current smoking by baseline eGFR strata (≥ 90 , 60-89 and < 60).

We first evaluated longitudinal eGFR changes over an 11-year study period. For each person, a simple linear regression of their log-transformed eGFR with years of follow-up from baseline as a predictor was conducted. After examining the linear trend of eGFR over time, the annual eGFR percent change was calculated using this formula: $(\exp(\log \text{ gfrslp}) - 1) * 100\%$, where $\log \text{ gfrslp}$ was the estimate of change in log-

transformed eGFR per year obtained from the linear regression. Individuals were then classified according to whether the annual eGFR declined by >3%. Multivariable logistic regression models were constructed to evaluate the association of potential risk factors with the odds of annual eGFR decline >3%. Potential risk factors examined were baseline characteristics: HIV/HAART status (3 groups: HIV- [reference], HIV+ no-HAART, HIV+ HAART), eGFR categories (<60, 60-89, \geq 90 [reference]), age (<40 [reference], 40-49, 50-59, \geq 60), race (White [reference], African-American, and Hispanic or other race), a history of diabetes, a history of hypertension, cigarette smoking status (current, former, never [reference]), HBV and/or HCV infection. Cohort entry status (pre-2001 [reference] vs. 2001-03 cohort) was included to control for additional differences in the cohorts, and the number of eGFR measurements contributed per person. Among HIV+ men, a history of a clinical AIDS diagnosis, baseline CD4+ T-cell counts (\leq 200, 201-350, 351-500, and $>$ 500 cells/mm³[reference]) and detectable plasma HIV RNA (\geq 50 copies/mL) levels were also evaluated in association with eGFR decline. Among HIV+ HAART-users, years from HAART initiation to baseline and cumulative years on individual antiretroviral drugs from HAART initiation to baseline were also examined in separate models. Baseline eGFR levels and age were fixed in the final model; other factors with a p-value <0.1 were kept in the final multivariable model.

We then measured the prevalence of confirmed proteinuria, defined as a UPCR \geq 0.2 at two consecutive visits (no more than 1 year apart), and evaluated factors associated with confirmed proteinuria among HIV+ and HIV- participants from April 2006 (when UPCR measurements were added to the protocol) through September 2014. This definition of proteinuria was used in order to minimize the likelihood that the

presence of proteinuria was due to a transient process not related to chronic kidney disease. Multivariable logistic regression models were used to determine factors associated with proteinuria. In this analysis, except for HIV/HAART status and baseline eGFR, other exposure variables were time-varying and included those taken from the visit ($V_{(i-1)}$) prior to the first visit of the visit-pairs at which proteinuria was assessed. Potential risk factors considered in these models included those present in the eGFR analyses, as well as the presence of annual eGFR decline $>3\%$ from baseline to $V_{(i)}$. Separate models were constructed for HAART-users when examining specific antiretroviral drugs. Generalized estimating equations (GEE) were used to analyze longitudinal data with repeated measures.

We also examined whether proteinuria predicted eGFR change. The key exposure variable here was proteinuria, and the outcome variable was annual eGFR decline $>3\%$ in the next year (i.e., the calculation was based on three eGFRs: GFR at the current visit [$V_{(i)}$ when proteinuria was determined] and the two visits that followed). Other exposure variables adjusted in multivariable logistic regression models were similar to the previous analysis of proteinuria, but were taken at $V_{(i)}$.

Multiple imputation was performed for missing risk factor data in multivariable models. For each outcome, the multiple imputation included all predictors and the outcome. Missing values were imputed 5 times on the basis of the distribution of covariates by using a Markov-Chain Monte Carlo method assuming multivariable normality^[22]. Missing values were imputed for multiple regression analyses for smoking status (2% of all person-visits data for analysis), CD4 cell count ($<1\%$ among HIV+),

HIV RNA (<1% among HIV+), HCV-infection (<1%), and HBV-infection (<1%). All analyses were done by using SAS 9.2 (SAS Institute, Cary, North Carolina, USA).

Evaluation of hsCRP

We cross-sectionally evaluated high sensitivity C-reactive protein (hsCRP) serum levels which were available from specimens drawn at routine visits during April to September 2006, to assess associations of systemic inflammation with eGFR and proteinuria.

Results

Baseline Characteristics

We analyzed eGFR changes among 2381 men. At baseline, 1305 (54%) men were HIV-, 917 (39%) were HIV+ and had initiated HAART, and 159 (7%) were HIV+ and HAART-naïve (Table 1). Among the 917 HAART users in our study, 60 were pre-HAART ART-experienced. Table 1 shows differences in baseline characteristics in these patient groups with regard to hypertension, diabetes, HBV and HCV serostatus, and HIV clinical indicators.

Risk Factors and Estimated GFR at Baseline

Median baseline eGFR was 90 for HIV- men, 94 for HIV+ HAART-users, and 97 for HIV+ HAART-naïve men ($p=0.004$ for HIV- vs. HIV+ HAART-users, $p<0.001$ for HIV- vs. HIV+ HAART-naïve men). The proportion of men with baseline eGFR <60 was higher among HIV+ men receiving HAART (6%) than HIV- men (4%, $p<0.001$).

The prevalence of hypertension (56%, 74%, and 88%, respectively; $p<0.001$ for trend) and of diabetes (9%, 11%, and 27%, respectively; $p<0.001$ for trend) increased while current smoking prevalence decreased (40%, 23% and 18%, respectively; $p<0.001$ for trend) incrementally with lower baseline eGFR strata (≥ 90 , 60-89 and <60).

Association of Baseline Clinical Factors with Longitudinal Estimated GFR

The median number of eGFR assessments performed per person during the 11-year follow-up period was 19 for HIV- men, 19 for HIV+ HAART-users, and 7 for HIV+ HAART-naïve men. Median annual eGFR change was -0.5% overall, -0.8% for HIV+ men and -0.3% for HIV- men ($p<0.001$). A 3% annual decline in eGFR represented approximately the lowest 15th percentile of the range of observed changes.

For examining change in eGFR, men aged 50-59 and ≥ 60 years at baseline demonstrated similar trends, so were combined in the final multivariable model. Factors independently associated with $>3\%$ annual eGFR decline included: HIV+ HAART+, age ≥ 50 , current smoking, a history of diabetes or hypertension, HCV infection, and MACS enrollment in 2001-03 (versus earlier, Table 2). Men with baseline eGFR 60-89 (compared to ≥ 90), Hispanic or other race (compared to White) and men with more eGFR measurements were less likely to have $>3\%$ annual eGFR decline. In this model, HBV infection, a history of AIDS, CD4 cell count, and detectable HIV RNA were not independently associated with eGFR decline. Among HAART-users, no specific antiretroviral drug use before baseline was independently associated with eGFR decline over the 11-year study period after adjusting for factors included in previous model.

Proteinuria Analysis

Proteinuria was detected in 1613 (7%) of 22,177 person-visit pairs: 243 (2%) of person-visit pairs from 64 HIV- men, 1337 (15%) of person-visit pairs from 260 HIV+ HAART-users, and 33 (6%) of person-visit-pairs from 9 HIV+ HAART-naive men.

Proteinuria was observed in 522 person-visit-pairs (36%) of the eGFR<60 group, 694(7%) of the eGFR 60-90 group, and 397 (4%) of the eGFR>90 group (Figure). Within each eGFR stratum, proteinuria occurred more frequently among HIV+ HAART-users than HIV- men (all $P<0.01$). Among 2059 men with at least three eGFR measurements and at least two urine UPCR measurements performed at two consecutive visits over the 8-year period of follow-up, men with annual eGFR declines of $>3\%$ more often exhibited proteinuria in at least one visit pair (45%) than their counterparts (12%, OR= 5.8, $p<0.001$).

As shown in Table 3, factors independently associated with proteinuria were: 1) a baseline eGFR 60-90 or <60, versus >90; 2) $\geq 3\%$ annual decline in eGFR; 3) HIV infection with HAART use; 4) age ≥ 50 vs. <40 at the visit prior to proteinuria detection ($V_{(i-1)}$); 5) presence of any of the following at the $V_{(i-1)}$ visit: a history of diabetes or hypertension, current smoking, HCV infection, or a CD4 ≤ 200 or 201-500 (vs. >500). Among HAART-users, use of didanosine, saquinavir or nelfinavir were additionally positively associated with proteinuria, while lamivudine use appeared protective.

The median eGFR decline was significantly ($p<0.001$) greater following confirmed proteinuria (-2.0% per year) than observed among those without proteinuria (-0.70% per year). The unadjusted odds ratios of having a subsequent annual eGFR decline of $>3\%$ among persons with proteinuria versus without proteinuria were 1.74

(95% CI:1.42-2.13, $p<0.001$), 2.09 (95% CI: 1.79-2.46, $p<0.001$), and 2.38 (95% CI:1.84-3.07, $p<0.001$) for men with GFR ≥ 90 , 60-89, and <60 at $V_{(i)}$, respectively. However, of the 1613 person-visit pairs with proteinuria, 39% had eGFR annual decline $>3\%$ before proteinuria was measured, while only 12% had prior eGFR annual decline $>3\%$ of 20,564 person-visit pairs without proteinuria. Table 4 illustrates that proteinuria was significantly associated with subsequent eGFR decline ($>3\%$) in the following year, after adjusting for other factors significantly associated with eGFR decline: a beginning eGFR >90 , HIV infection, HAART receipt, age >40 , cohort entered study in 2001-03, and a history of diabetes or hypertension. Inclusion of CD4+ cell count in the multivariable model did not attenuate the association between proteinuria and subsequent eGFR decline (OR=1.77, 95% CI: 1.56-2.01). In addition, among HAART-users, a detectable HIV RNA, cumulative use of tenofovir disoproxil fumarate, emtricitabine, ritonavir, atazanavir, any PI, or fluconazole were positively associated with a subsequent eGFR annual decline of $>3\%$ in separate models adjusting for proteinuria, HIV/HAART status, baseline eGFR level, age, race, cohort entry, and a history of diabetes or hypertension. The association of proteinuria with subsequent eGFR decline $>3\%$ tended to be stronger in men with eGFR <90 (Table 5).

CRP Sub-Analysis

For the 12,608 UPCR person-visit-pairs at which CRP was measured, adding CRP (categorized as <1 , 1-3, ≥ 3) to the final model revealed adjusted ORs for proteinuria of 1.70 (95% CI: 1.12-2.59) and 1.97 (95% CI: 1.28-3.02) for men with CRP levels of 1-3 mg/L and ≥ 3 mg/L vs. <1 mg/L), respectively. Similarly, men with a CRP level ≥ 3 (vs.

<1) were more likely to have a subsequent eGFR decline of >3% in the next year after adjusting for proteinuria and other factors in the final model (OR=1.13 (95% CI: 1.02-1.26).

Discussion

In this well-characterized, prospectively followed cohort of HIV-infected and uninfected men, we observed that declines in eGFR over an 11-year period were not clearly associated with HIV serostatus (though we studied few HIV+ persons not receiving HAART) per se but were positively associated with HAART use in general. While HIV-infected HAART-recipients more often had low baseline kidney function (eGFR <60) than HIV-uninfected men, proteinuria was nearly 7 times more common in HAART-treated HIV-infected than HIV-uninfected men. In addition proteinuria was more common among HIV-infected persons than were eGFR declines, and was concurrent with recent eGFR declines and highly predictive of subsequent eGFR declines. Proteinuria was also associated with historical exposure to didanosine, saquinavir or, and nelfinavir use, and positively correlated with systemic inflammation. Not unexpectedly, proteinuria was likewise more common in men with classic risk factors for kidney disease, such as hypertension, diabetes mellitus, and tobacco smoking.

Longitudinal measurements of eGFR and concurrent serial assessments of proteinuria were available and, among HIV-infected persons on HAART, in analytic models that included adjustment for the presence of proteinuria, our observed associations of

cumulative use of TDF, emtricitabine, ritonavir, atazanavir, any PI, or fluconazole with eGFR declines in the following year, were noteworthy. Associations between TDF use and GFR declines have been well-described in other cohorts^[23-25]. Such declines are not always reversible^[26, 27], may be cumulative, and may result in drug discontinuation. During the 11-year study period, HIV-infected participants often switched their HAART regimen over time (data not presented), which could have affected their subsequent eGFR levels. This may partly explain why no associations were seen between individual antiretroviral drugs used before baseline and the eGFR decline over the 11-year period. Recent data from other cohorts have indicated associations between cumulative atazanavir use and kidney function decline^[28-32]. While our observed association between ritonavir use and eGFR decline was not unanticipated because of the drug's inhibition of renal tubular creatinine secretion, eGFR declines may also have occurred because of ritonavir's intended effects of increasing levels of atazanavir and of TDF, both drugs that can exhibit dose-dependent nephrotoxicity^[33]. The association of emtricitabine use with eGFR decline likely reflects the fact that it was virtually always co-prescribed with TDF during the time period included in this study, and vice-versa, and rather than emtricitabine-induced adverse kidney effects. While our observed association between fluconazole use and eGFR decline was not expected, it may be related to the fact that fluconazole (both in the general HIV+ population as well as in our cohort) has been most often associated with having more advanced HIV infection (data not shown), higher plasma HIV viremia and lower CD4 count, all factors associated historically with worse kidney function among HIV+ persons. The same principle may have been operative in our finding of the association between historical exposure to didanosine, saquinavir or

nelfinavir with proteinuria; all of these were antiretroviral drugs used primarily in the early HAART era among patients who in general had more advanced HIV infection than more recent HAART-initiators. It is possible, though, that unmeasured indices of overall health may have influenced our observed associations between use of specific antiretroviral drugs with proteinuria and/or eGFR declines, despite having controlled for stage of HIV disease and the presence of important co-morbid diseases [34, 35].

The strong associations observed between proteinuria and HIV infection, HAART use, and more rapid declines in eGFR, were less pronounced but still apparent even among persons with baseline eGFRs in the normal range and support the hypothesis that proteinuria is concurrent with and predictive of kidney disease among HIV+ persons^[36, 37]. We found that proteinuria was strongly predictive of subsequent eGFR decline over the next year, a finding that has been identified in HIV-uninfected populations^[38-41]. Furthermore, the observed associations of known non-HIV causes of kidney disease (such as hypertension and diabetes) and proteinuria in our cohort are consonant with observations from other cohorts of HIV+ persons^[1, 42-45], attesting to the sensitivity of proteinuria as a marker of incipient decline in GFR^[11]. The extent to which and how HIV infection, specific antiretroviral drug use, and these other co-morbidities may interact to hasten the onset of proteinuria among HIV+ persons with other risk factors for kidney disease, is unclear. Nevertheless, the identification of proteinuria as a marker of eGFR decline may have implications for future research seeking to evaluate whether or not, among HIV-infected persons, specific therapeutic drug interventions for hypertension (such as ACE-inhibitors/ angiotensin receptor blockers) can ameliorate proteinuria-

associated declines in kidney function, as has been observed in some subgroups of the proteinuric general population.

Our finding of a positive association between plasma CRP levels and proteinuria suggests that the latter is positively linked to the presence of systemic inflammation. The increased likelihood of proteinuria observed among persons in our cohort who had co-existing chronic systemic illnesses associated with increased inflammation such as diabetes mellitus, as well as its positive association with tobacco smoking, support this hypothesis. Furthermore, our finding that, even in the presence of these co-morbid conditions, more advanced HIV infection remained independently associated with proteinuria and declines in kidney function, also supports an etiologic link between chronic systemic inflammation and proteinuria. Other recent work from our group and others supports this^[11, 46, 47]. The proportional contributions of HIV infection, specific antiretroviral drug use, and the presence of inciting co-morbid diseases toward the development of kidney disease (as evidenced by either proteinuria and eGFR decline) probably varies from individual to individual and likely has much to do with the severity and chronicity of the underlying systemic diseases as well as the success of medical management of each of the component illnesses.

In the overall cohort, we noted anticipated associations between eGFR declines, proteinuria and older age over the 11-year time period of observation represented in this report. Age-associated declines in eGFR have become more apparent in analyses of cohorts with longer periods of follow-up. Furthermore, the association between higher baseline eGFR (>90) with increased likelihood for subsequent declines in eGFR (Table 2) at first glance seems counterintuitive, but: 1) may reflect fact that persons with higher

GFRs have greater room for decline, particularly since, in general, we did not find differentially higher rates of non-HIV risks for kidney disease among persons with higher baseline eGFRs and; 2) may possibly be related to the phenomenon of hyperfiltration, which has been linked to more rapid subsequent kidney function decline among HIV+ persons^[48, 49].

Limitations to this analysis exist. There may have been factors influencing eGFR decline that we did not or could not directly measure. Also, determinations of relationships between specific antiretroviral use and eGFR declines or proteinuria can be complex. Most of our measurements were made while persons were already receiving HAART; most of these regimens did not constitute a given patient's first exposure to antiretrovirals. Previously received antiretrovirals were not taken into account, and we did not evaluate pre-HAART eGFRs systematically. This analysis reflects persons who entered care prior to 2003 and stayed in care for 11 years and may not be generalizable to persons who more newly entered care. Also, our report is subject to limitations that are inherent to analyses of any observational cohort. Another potential limitation is the inherent inaccuracy of eGFRs, even those based upon the most modern estimating equations, particularly among persons with higher true GFRs^[50].

These observations support current clinical practices that include aggressive control of both HIV infection and any co-morbid conditions that are known to result in impaired renal function over time. Given the high and growing prevalence of traditional risk factors for chronic kidney disease among aging HAART-treated HIV+ persons, our findings support current recommendations advising that screening for kidney disease in HIV-infected persons should include routine assessments of both eGFR and proteinuria,

with the latter often providing the first indication that kidney dysfunction is present. Furthermore, our findings indicate that, among HIV+ persons with proteinuria, cumulative use of specific antiretrovirals, notably TDF and atazanavir may contribute to GFR decline. The extent to which these observations should inform antiretroviral selection, particularly among aging HIV+ persons with competing risks for kidney disease, and whether the current widespread use of newer antiretrovirals such tenofovir alafenamide that have fewer adverse renal effects or the use of NRTI-sparing HAART will ameliorate the burden of HIV-related renal disease over time, requires further evaluation and will be the subject of future work from our group.

Table 1. Baseline characteristics of study population

Characteristics	HIV-	HIV+ HAART+	HIV+ HAART-	Overall
Number of participants	1305	917	159	2381
Age (years), N(%)				
<40	256(20)	224(24)	49(31)	529(22)
40-49	446(34)	400(44)	60(38)	906(38)
50-59	419(32)	244(27)	46(29)	709(30)
>=60	184(14)	49(5)	4(3)	237(10)
Race, N(%)				
African American	263(20)	256(28)	65(41)	584(25)
Caucasian	916(70)	514(56)	72(45)	1502(63)
Hispanic	108(8)	132(14)	22(14)	262(11)
Other	18(1)	15(2)	0(0)	33(1)
Estimated GFR (mL/min per 1.73 m ²), N(%)				
<60	46(4)	54(6)	1(1)	101(4)
60-89	595(46)	342(37)	55(35)	992(42)
>=90	664(51)	521(57)	103(65)	1288(54)
History of diabetes, N(%)	110(8)	132(14)	13(8)	255(11)
History of hypertension, N(%)	873(67)	583(64)	86(54)	1542(65)
Tobacco use, N(%)				
Current	370(29)	312(34)	68(44)	750(32)
Former	565(44)	365(40)	48(31)	978(42)
HCV-infection, N(%)	61(5)	92(10)	16(10)	169(7)
HBV-infection, N(%)	18(1)	44(5)	11(7)	73(3)
Cohort Entry Year, N(%)				
Pre-2001	844(65)	479(52)	71(45)	1394(59)
2001-03	461(35)	438(48)	88(55)	987(41)
Number of eGFR contributed during study	19(11-21)	19(11-21)	7(4-12)	18(10-21)
CD4 count (cells/uL), median (IQR)		499(344-677)	534(403-733)	
Nadir CD4 count (cells/uL), median (IQR)		248(130-355)	441(329-591)	
HIV RNA (copies/mL), median (IQR)		<50(<50-1460)	8468(512-29687)	
Undetectable HIV RNA, N(%)		552(60)	16(10)	
AIDS, N(%)		135(15)	2(1)	
% of ever used ARV; median (IQR) of cumulative years on ARV				

Characteristics	HIV-	HIV+ HAART+	HIV+ HAART-	Overall
Zidovudine (AZT)		79%;3.1(1.2-5.5)		
Zalcitabine (DDC)		18%;0.9(0.3-1.8)		
Didanosine (DDI)		44%;1.5(0.6-3.3)		
Stavudine (D4T)		62%;3(1.4-5.2)		
Lamivudine (3TC)		92%;3.9(1.9-6)		
Abacavir (ABC)		39%;1.5(0.6-2.9)		
Tenofovir disoproxil fumarate (TDF)		31%;0.9(0.5-1.4)		
Emtricitabine (FTC)		2%;0.4(0.2-2.2)		
Saquinavir (SQV)		25%;1.5(0.6-3.4)		
Ritonavir (RTV)		43%;1.9(0.6-3.4)		
Indinavir (IDV)		40%;2.5(0.9-4.8)		
Nelfinavir (NFV)		36%;1.6(0.5-3.6)		
Lopinavir (LPV)		22%;1.3(0.5-2.1)		
Amprenavir (APV)		8%;1.5(0.6-3)		
Atazanavir (ATZ)		3%;0.4(0.2-0.9)		
Nevirapine (NVP)		32%;1.5(0.5-3.6)		
Delavirdine (DLV)		3%;0.7(0.2-1.8)		
Efavirenz (EFV)		47%;1.9(0.7-3.3)		
Enfuvirtide (T-20) use		1%;0.4(0.3-1.8)		
Raltegravir		0.4%;0.8(0.3-2)		
Elvitegravir (including Stribild)		0%;		
Dolutegravir (including Triumeq)		0%;		
Fluconazole (FLU)		19%;0.9(0.3-2.8)		
Protease inhibitors (PI)		73%;4.2(2.3-5.8)		
Non-nucleoside reverse transcriptase inhibitor (NNRTI)		69%;2.2(1-3.9)		
Nucleoside reverse transcriptase inhibitors (NRTI)		96%;5.9(3.3-8.5)		
Integrase Inhibitors		0.4%;0.8(0.3-2)		

IQR: Interquartile range

Table 2. Factors Associated with >3% Annual GFR Decline over an 11-year period among 2381 men

Factors	Unadjusted OR(95% CI)	p-value	Adjusted OR(95% CI)	p-value
HIV/HAART status at baseline				
HIV-	1.00(ref)		1.00(ref)	
HIV+, HAART-	2.20(1.37,3.53)	0.001	1.25(0.76,2.07)	0.377
HIV+, HAART+	2.86(2.21,3.71)	<0.001	2.91(2.21,3.83)	<0.001
Baseline eGFR(mL/min per 1.73m ²)				
≥90	1.00(ref)		1.00(ref)	
60-89	0.76(0.59,0.98)	0.034	0.76(0.57,1.02)	0.063
<60	1.75(1.06,2.88)	0.028	1.30(0.75,2.28)	0.351
Baseline age (years)				
<40	1.00(ref)		1.00(ref)	
40-49	1.09(0.78,1.51)	0.621	1.22(0.83,1.79)	0.314
≥50	1.15(0.83,1.58)	0.405	1.60(1.02,2.51)	0.039
Race				
White	1.00(ref)		1.00(ref)	
Black	1.67(1.29,2.18)	<0.001	1.13(0.80,1.59)	0.503
Hispanice/Other	0.77(0.50,1.18)	0.227	0.59(0.36,0.95)	0.030
History of diabetes	2.29(1.66,3.15)	<0.001	1.90(1.35,2.69)	<0.001
History of hypertension	1.60(1.22,2.09)	<0.001	1.73(1.26,2.36)	<0.001
Smoking status				
Never	1.00(ref)		1.00(ref)	
Current	1.92(1.38,2.67)	<0.001	1.46(1.02,2.09)	0.039
Former	1.35(0.97,1.89)	0.073	1.21(0.86,1.71)	0.274
HCV-infection	2.53(1.75,3.66)	<0.001	1.49(0.98,2.28)	0.064
Number of eGFR contributed,per 1 count	0.93(0.91,0.94)	<0.001	0.92(0.90,0.94)	<0.001
Cohort entry 2001-03	1.34(1.05,1.70)	0.018	1.48(1.03,2.14)	0.036

Table 3. Factors Associated with confirmed Proteinuria^{#*^}

Factors	Unadjusted OR(95% CI)	p-value	Adjusted OR(95% CI)	p-value
HIV/HAART status at baseline				
HIV-	1.00(ref)		1.00(ref)	
HIV+, HAART-	3.16(1.29,7.75)	0.012	3.28(1.29,8.34)	0.012
HIV+, HAART+	8.93(6.19,12.87)	<0.001	6.99(4.72,10.36)	<0.001
Baseline eGFR(mL/min per 1.73m ²)				
≥90	1.00(ref)		1.00(ref)	
60-89	1.27(0.94,1.72)	0.118	1.57(1.14,2.18)	0.006
<60	4.45(2.74,7.24)	<0.001	4.15(2.52,6.84)	<0.001
eGFR decline >3% per year	4.75(3.69,6.11)	<0.001	3.80(2.90,4.98)	<0.001
Age (years)				
<40	1.00(ref)		1.00(ref)	
40-49	2.61(1.38,4.94)	0.003	1.39(0.71,2.71)	0.337
≥50	3.47(1.82,6.63)	<0.001	2.04(1.01,4.08)	0.045
History of diabetes	3.29(2.48,4.36)	<0.001	2.35(1.75,3.17)	<0.001
History of hypertension	2.32(1.60,3.36)	<0.001	1.92(1.31,2.79)	<0.001
Smoking status				
Never	1.00(ref)		1.00(ref)	
Current	2.04(1.39,2.99)	<0.001	1.82(1.20,2.76)	0.005
Former	1.21(0.84,1.75)	0.295	1.19(0.82,1.72)	0.369
HCV-infection	3.63(2.48,5.33)	<0.001	2.13(1.36,3.32)	<0.001
CD4+ T-cell count(cells/μl)				
>500	1.00(ref)		1.00(ref)	
201-500	3.46(2.71,4.42)	<0.001	1.26(0.97,1.62)	0.078
≤200	4.96(3.18,7.75)	<0.001	1.86(1.13,3.08)	0.015
Among HAART users				
Use of didanosine*	1.09(1.04,1.15)	<0.001	1.11(1.04,1.17)	<0.001
Use of lamivudine*	0.98(0.94,1.02)	0.338	0.94(0.90,0.98)	0.004
Use of saquinavir*	1.12(1.03,1.20)	0.006	1.10(1.02,1.19)	0.013
Use of nelfinavir*	1.06(0.99,1.13)	0.102	1.09(1.03,1.15)	0.005

[#]Among 2059 Men Who Contributed 22177 Person-Visit-pairs

* Per year of drug use

[^] Urine Protein-to-Creatinine ≥0.2 at two consecutive visits (no more than 1 year apart)

Table 4. The Association between Proteinuria and Subsequent eGFR Annual Decline >3% in the following year^{#*^}

Factors	Unadjusted OR(95% CI)	p-value	Adjusted OR(95% CI)	p-value
Proteinuria	1.71(1.54,1.91)	<0.001	1.80(1.58,2.05)	<0.001
HIV/HAART status at baseline				
HIV-	1.00(ref)		1.00(ref)	
HIV+, HAART-	0.85(0.72,1.01)	0.058	0.83(0.70,0.99)	0.039
HIV+, HAART+	1.26(1.19,1.33)	<0.001	1.20(1.11,1.29)	<0.001
eGFR(mL/min per 1.73m2) [†]				
≥90	1.00(ref)		1.00(ref)	
60-89	0.69(0.64,0.74)	<0.001	0.62(0.57,0.67)	<0.001
<60	0.64(0.53,0.76)	<0.001	0.43(0.36,0.51)	<0.001
Age (years)				
<40	1.00(ref)		1.00(ref)	
40-49	1.17(1.06,1.31)	0.003	1.19(1.06,1.34)	0.004
50-59	1.12(1.01,1.24)	0.035	1.26(1.11,1.43)	<0.001
≥60	1.17(1.05,1.31)	0.005	1.52(1.31,1.75)	<0.001
Race				
White	1.00(ref)		1.00(ref)	
Black	1.19(1.11,1.27)	<0.001	1.04(0.95,1.13)	0.447
Hispanic/Other	0.89(0.81,0.98)	0.013	0.80(0.71,0.90)	<0.001
Cohort entry 2001-03	1.10(1.04,1.17)	<0.001	1.12(1.02,1.22)	0.013
History of diabetes	1.22(1.14,1.31)	<0.001	1.13(1.04,1.22)	0.003
History of hypertension	1.15(1.07,1.23)	<0.001	1.16(1.07,1.26)	<0.001
Among HAART users				
Detectable HIV RNA (≥50 vs. <50 copies/ml)	0.99(0.99,1.00)	0.237	1.18(1.04,1.33)	0.011
Use of zidovudine*	1.02(1.00,1.04)	0.011	0.99(0.98,1.00)	0.021
Use of tenofovir*	1.04(1.02,1.06)	<0.001	1.03(1.01,1.04)	0.002
Use of emtricitabine*	1.01(1.00,1.02)	0.172	1.05(1.03,1.07)	<0.001
Use of ritonavir*	1.02(1.00,1.04)	0.110	1.01(1.00,1.02)	0.084
Use of atazanavir*	1.03(1.00,1.05)	0.018	1.03(1.01,1.06)	0.007
Use of fluconazole*	1.03(0.99,1.07)	0.130	1.04(1.00,1.08)	0.072
Use of Protease Inhibitors*	1.01(1.00,1.02)	0.066	1.01(1.00,1.02)	0.070

[#]Among 1969 men who contributed 20331 Person-Visit-pairs with Urine Protein-to-Creatinine measured and 3 eGFR measurements in the following year

* Per year of drug use; each drug was examined in separate model adjusted for other factors listed in the Table.

^ Urine Protein-to-Creatinine ≥ 0.2

† At the visit when proteinuria was confirmed

Table 5. Association of proteinuria and subsequent eGFR decline>3% by eGFR level

	Prevalence of subsequent eGFR decline >3%		Adjusted* OR (95% CI) of subsequent eGFR decline >3% for proteinuria	P-value for the interaction of eGFR category and proteinuria
	Without Proteinuria	With Proteinuria		
eGFR<60	24%	43%	2.06 (1.43-2.97)	0.063
eGFR 60-90	31%	48%	1.88 (1.58-2.24)	0.175
eGFR ≥90	40%	54%	1.53(1.22-1.93)	(reference)

*Adjusted for HIV/HAART status, age, race, cohort status, history of diabetes, and history of hypertension.

CI: confidence interval

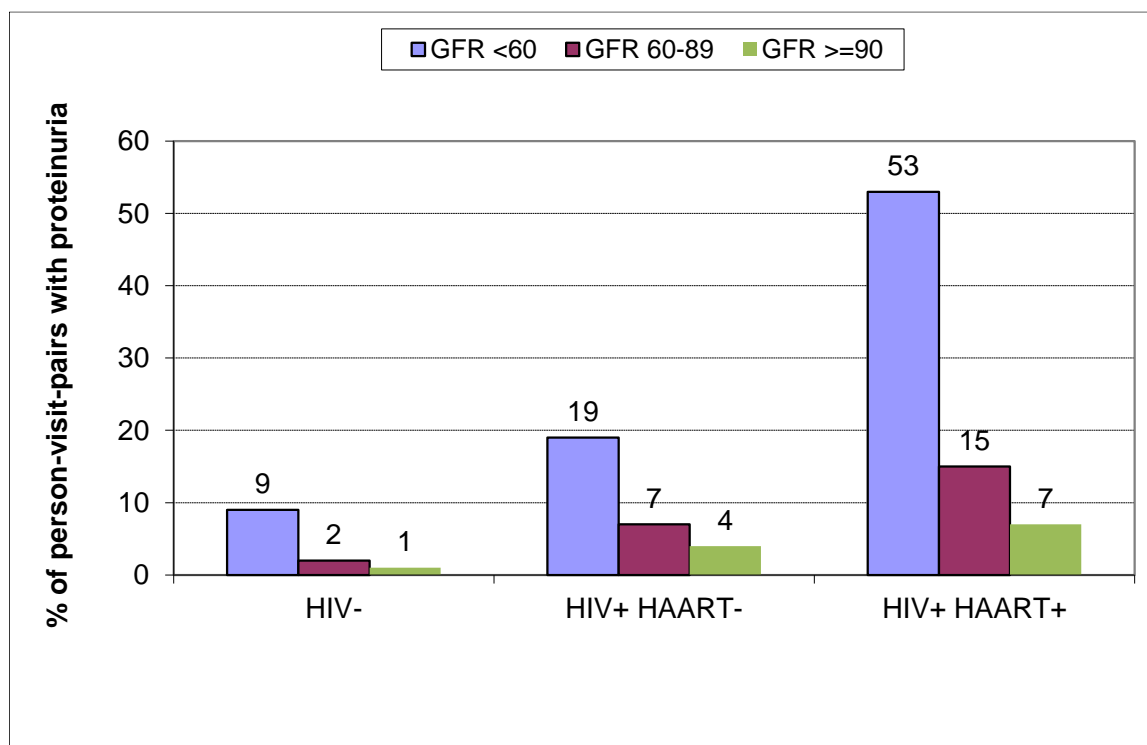


Figure: Relationship between Baseline GFR and Likelihood of Demonstrating Proteinuria During Follow-up, by HIV Serostatus and HAART Use Status

1. Choi AI, Li Y, Deeks SG, Grunfeld C, Volberding PA, Shlipak MG. **Association between kidney function and albuminuria with cardiovascular events in HIV-infected persons.** *Circulation* 2010; **121**(5):651-658.
2. Choi AI, Shlipak MG, Hunt PW, Martin JN, Deeks SG. **HIV-infected persons continue to lose kidney function despite successful antiretroviral therapy.** *AIDS* 2009; **23**(16):2143-2149.
3. George E, Lucas GM, Nadkarni GN, Fine DM, Moore R, Atta MG. **Kidney function and the risk of cardiovascular events in HIV-1-infected patients.** *AIDS* 2010; **24**(3):387-394.
4. Moso MA, Woolnough E, Langham F, Hoy JF, Cheng AC, Walker RG, et al. **Increasing prevalence and risk of chronic kidney disease in HIV-positive individuals: changing demographics over a six-year period.** *J Infect Dis* 2017.
5. Bruggeman LA, Ross MD, Tanji N, Cara A, Dikman S, Gordon RE, et al. **Renal epithelium is a previously unrecognized site of HIV-1 infection.** *J Am Soc Nephrol* 2000; **11**(11):2079-2087.
6. Lucas GM, Eustace JA, Sozio S, Mentari EK, Appiah KA, Moore RD. **Highly active antiretroviral therapy and the incidence of HIV-1-associated nephropathy: a 12-year cohort study.** *AIDS* 2004; **18**(3):541-546.
7. Cohen SD, Kopp JB, Kimmel PL. **Kidney Diseases Associated with Human Immunodeficiency Virus Infection.** *N Engl J Med* 2017; **377**(24):2363-2374.
8. Gameiro J, Jorge S, Lopes JA. **HIV and renal disease: a contemporary review.** *Int J STD AIDS* 2018;956462417750710.
9. Hou J, Nast CC. **Changing concepts of HIV infection and renal disease.** *Curr Opin Nephrol Hypertens* 2018.
10. Jotwani V, Atta MG, Estrella MM. **Kidney Disease in HIV: Moving beyond HIV-Associated Nephropathy.** *J Am Soc Nephrol* 2017; **28**(11):3142-3154.
11. Abraham AG, Darilay A, McKay H, Margolick JB, Estrella MM, Palella FJ, Jr., et al. **Kidney Dysfunction and Markers of Inflammation in the Multicenter AIDS Cohort Study.** *J Infect Dis* 2015; **212**(7):1100-1110.
12. Baxi SM, Scherzer R, Jotwani V, Estrella MM, Abraham AG, Parikh CR, et al. **Changes in Urinary Biomarkers Over 10 Years Is Associated With Viral Suppression in a Prospective Cohort of Women Living With HIV.** *J Acquir Immune Defic Syndr* 2017; **74**(5):e138-e145.
13. Jotwani V, Scherzer R, Estrella MM, Jacobson LP, Witt MD, Palella F, et al. **Association of HIV infection with biomarkers of kidney injury and fibrosis in the Multicenter AIDS Cohort Study.** *Antivir Ther* 2017; **22**(5):421-429.
14. Kooij KW, Vogt L, Wit F, van der Valk M, van Zoest RA, Goorhuis A, et al. **Higher Prevalence and Faster Progression of Chronic Kidney Disease in Human Immunodeficiency Virus-Infected Middle-Aged Individuals Compared With Human Immunodeficiency Virus-Uninfected Controls.** *J Infect Dis* 2017; **216**(6):622-631.
15. Ozanne A, Duffau P, Dauchy FA, Rigotherier C, Terrien C, Lazaro E, et al. **Activation, senescence and inflammation markers in HIV patients: association with renal function.** *AIDS* 2017; **31**(8):1119-1128.
16. Jotwani V, Scherzer R, Estrella MM, Jacobson LP, Witt MD, Palella F, et al. **Brief Report: Cumulative Tenofovir Disoproxil Fumarate Exposure is Associated With**

- Biomarkers of Tubular Injury and Fibrosis in HIV-Infected Men.** *J Acquir Immune Defic Syndr* 2016; **73**(2):177-181.
17. Jotwani V, Scherzer R, Estrella MM, Jacobson LP, Witt MD, Palella FJ, Jr., et al. **HIV Infection, Tenofovir, and Urine alpha1-Microglobulin: A Cross-sectional Analysis in the Multicenter AIDS Cohort Study.** *Am J Kidney Dis* 2016; **68**(4):571-581.
18. Kopp JB. **Chronic Kidney Disease in the Aging Human Immunodeficiency Virus-Infected Population.** *J Infect Dis* 2017; **216**(6):619-621.
19. Levey AS, Coresh J, Balk E, Kausz AT, Levin A, Steffes MW, et al. **National Kidney Foundation practice guidelines for chronic kidney disease: evaluation, classification, and stratification.** *Ann Intern Med* 2003; **139**(2):137-147.
20. Kaslow RA, Ostrow DG, Detels R, Phair JP, Polk BF, Rinaldo CR, Jr. **The Multicenter AIDS Cohort Study: rationale, organization, and selected characteristics of the participants.** *Am J Epidemiol* 1987; **126**(2):310-318.
21. Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF, 3rd, Feldman HI, et al. **A new equation to estimate glomerular filtration rate.** *Ann Intern Med* 2009; **150**(9):604-612.
22. Schafer JL, Olsen MK. **Multiple Imputation for Multivariate Missing-Data Problems: A Data Analyst's Perspective.** *Multivariate Behav Res* 1998; **33**(4):545-571.
23. Gallant JE, Moore RD. **Renal function with use of a tenofovir-containing initial antiretroviral regimen.** *AIDS* 2009; **23**(15):1971-1975.
24. Horberg M, Tang B, Towner W, Silverberg M, Bersoff-Matcha S, Hurley L, et al. **Impact of tenofovir on renal function in HIV-infected, antiretroviral-naïve patients.** *J Acquir Immune Defic Syndr* 2010; **53**(1):62-69.
25. Mocroft A, Kirk O, Reiss P, De Wit S, Sedlacek D, Beniowski M, et al. **Estimated glomerular filtration rate, chronic kidney disease and antiretroviral drug use in HIV-positive patients.** *AIDS* 2010; **24**(11):1667-1678.
26. Kinai E, Hanabusa H. **Progressive renal tubular dysfunction associated with long-term use of tenofovir DF.** *AIDS Res Hum Retroviruses* 2009; **25**(4):387-394.
27. Scherzer R, Estrella M, Li Y, Choi AI, Deeks SG, Grunfeld C, et al. **Association of tenofovir exposure with kidney disease risk in HIV infection.** *AIDS* 2012; **26**(7):867-875.
28. Cure S, Bianic F, Espinas C, Hardy H, Rosenblatt L, Juday T. **Systematic Literature Review and Meta-Analysis of Renal Function in Human Immunodeficiency Virus (HIV)-Infected Patients Treated with Atazanavir (ATV)-Based Regimens.** *PLoS One* 2015; **10**(5):e0124666.
29. Gervasoni C, Meraviglia P, Minisci D, Ferraris L, Riva A, Landonio S, et al. **Metabolic and kidney disorders correlate with high atazanavir concentrations in HIV-infected patients: is it time to revise atazanavir dosages?** *PLoS One* 2015; **10**(4):e0123670.
30. Hara M, Suganuma A, Yanagisawa N, Imamura A, Hishima T, Ando M. **Atazanavir nephrotoxicity.** *Clin Kidney J* 2015; **8**(2):137-142.
31. Ryom L, Mocroft A, Kirk O, Worm SW, Kamara DA, Reiss P, et al. **Association between antiretroviral exposure and renal impairment among HIV-positive persons with normal baseline renal function: the D:A:D study.** *J Infect Dis* 2013; **207**(9):1359-1369.

32. Young J, Schafer J, Fux CA, Furrer H, Bernasconi E, Vernazza P, et al. **Renal function in patients with HIV starting therapy with tenofovir and either efavirenz, lopinavir or atazanavir.** *AIDS* 2012; **26**(5):567-575.
33. Calza L, Trapani F, Salvadori C, Magistrelli E, Manfredi R, Colangeli V, et al. **Incidence of renal toxicity in HIV-infected, antiretroviral-naïve patients starting tenofovir/emtricitabine associated with efavirenz, atazanavir/ritonavir, or lopinavir/ritonavir.** *Scand J Infect Dis* 2013; **45**(2):147-154.
34. Lucas GM, Ross MJ, Stock PG, Shlipak MG, Wyatt CM, Gupta SK, et al. **Clinical practice guideline for the management of chronic kidney disease in patients infected with HIV: 2014 update by the HIV Medicine Association of the Infectious Diseases Society of America.** *Clin Infect Dis* 2014; **59**(9):e96-138.
35. Mocroft A, Lundgren J, Ross M, Law M, Reiss P, Kirk O, et al. **A clinically useful risk-score for chronic kidney disease in HIV infection.** *J Int AIDS Soc* 2014; **17**(4 Suppl 3):19514.
36. Berhane AM, Weil EJ, Knowler WC, Nelson RG, Hanson RL. **Albuminuria and estimated glomerular filtration rate as predictors of diabetic end-stage renal disease and death.** *Clin J Am Soc Nephrol* 2011; **6**(10):2444-2451.
37. Sarnak MJ, Astor BC. **Implications of proteinuria: CKD progression and cardiovascular outcomes.** *Adv Chronic Kidney Dis* 2011; **18**(4):258-266.
38. **Chapter 2: Definition, identification, and prediction of CKD progression.** *Kidney Int Suppl* (2011) 2013; **3**(1):63-72.
39. Halbesma N, Kuiken DS, Brantsma AH, Bakker SJ, Wetzels JF, De Zeeuw D, et al. **Macroalbuminuria is a better risk marker than low estimated GFR to identify individuals at risk for accelerated GFR loss in population screening.** *J Am Soc Nephrol* 2006; **17**(9):2582-2590.
40. Hirayama A, Konta T, Kamei K, Suzuki K, Ichikawa K, Fujimoto S, et al. **Blood Pressure, Proteinuria, and Renal Function Decline: Associations in a Large Community-Based Population.** *Am J Hypertens* 2015; **28**(9):1150-1156.
41. Hunsicker LG, Adler S, Caggiula A, England BK, Greene T, Kusek JW, et al. **Predictors of the progression of renal disease in the Modification of Diet in Renal Disease Study.** *Kidney Int* 1997; **51**(6):1908-1919.
42. Gupta SK, Smurzynski M, Franceschini N, Bosch RJ, Szczech LA, Kalayjian RC, et al. **The effects of HIV type-1 viral suppression and non-viral factors on quantitative proteinuria in the highly active antiretroviral therapy era.** *Antivir Ther* 2009; **14**(4):543-549.
43. Szczech LA, Grunfeld C, Scherzer R, Canchola JA, van der Horst C, Sidney S, et al. **Microalbuminuria in HIV infection.** *AIDS* 2007; **21**(8):1003-1009.
44. Wyatt CM, Hoover DR, Shi Q, Seaberg E, Wei C, Tien PC, et al. **Microalbuminuria is associated with all-cause and AIDS mortality in women with HIV infection.** *J Acquir Immune Defic Syndr* 2010; **55**(1):73-77.
45. Yanik EL, Lucas GM, Vlahov D, Kirk GD, Mehta SH. **HIV and proteinuria in an injection drug user population.** *Clin J Am Soc Nephrol* 2010; **5**(10):1836-1843.
46. Baekken M, Os I, Sandvik L, Oektedalen O. **Microalbuminuria associated with indicators of inflammatory activity in an HIV-positive population.** *Nephrol Dial Transplant* 2008; **23**(10):3130-3137.

47. Gupta SK, Kitch D, Tierney C, Melbourne K, Ha B, McComsey GA, et al. **Markers of renal disease and function are associated with systemic inflammation in HIV infection.** *HIV Med* 2015; **16**(10):591-598.
48. Ng DK, Jacobson LP, Brown TT, Palella FJ, Jr., Martinson JJ, Bolan R, et al. **HIV therapy, metabolic and cardiovascular health are associated with glomerular hyperfiltration among men with and without HIV infection.** *AIDS* 2014; **28**(3):377-386.
49. Palatini P. **Glomerular hyperfiltration: a marker of early renal damage in pre-diabetes and pre-hypertension.** *Nephrol Dial Transplant* 2012; **27**(5):1708-1714.
50. Margolick JB, Jacobson LP, Schwartz GJ, Abraham AG, Darilay AT, Kingsley LA, et al. **Factors affecting glomerular filtration rate, as measured by iohexol disappearance, in men with or at risk for HIV infection.** *PLoS One* 2014; **9**(2):e86311.